Pulmonary gas exchange in Andean natives with excessive polycythemia—effect of hemodilution

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MANIER, GÉRARD, HERVÉ GUENARD, YVES CASTAING, NICOLE VARENE, AND ENRIQUE VARGAS. *Pulmonary gas exchange in Andean natives with excessive polycythemia—effect of hemodilution.* J. Appl. Physiol. 65(5): 2107–2117, 1988.—Pulmonary gas exchange in Andean natives ($n = 8$) with excessive high-altitude (3,600–4,200 m) polycythemia (hematocrit $65.1 \pm 6.6\%$) and hypoxemia (arterial P_{O_2} 45.6 ± 5.6 Torr) in the absence of pulmonary or cardiovascular disease was investigated both before and after isovolemic hemodilution by use of the inert gas elimination technique. The investigations were carried out in La Paz, Bolivia (3,650 m, 500 mmHg barometric pressure). Before hemodilution, a low ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mode ($\dot{V}_A/\dot{Q} < 0.1$) without true shunt accounted for $11.6 \pm 5.5\%$ of the total blood flow and was mainly responsible for the hypoxemia. The hypoventilation with a low mixed venous P_{O_2} value may have contributed to the observed hypoxemia in the absence of an impairment in alveolar capillary diffusion. After hemodilution, cardiac output and ventilation increased from 5.5 ± 1.2 to 6.9 ± 1.2 l/min and from 8.5 ± 1.4 to 9.6 ± 1.3 l/min, respectively, although arterial and venous P_{O_2} remained constant. $\dot{V}_A/\dot{Q}$ mismatching fell slightly but significantly. The hypoxemia observed in subjects suffering from high-altitude excessive polycythemia was attributed to an increased in blood flow perfusing poorly ventilated areas, but without true intra- or extrapulmonary shunt. Hypoventilation as well as a low mixed venous P_{O_2} value may also have contributed to the observed hypoxemia.

chronic mountain sickness; secondary polycythemia; ventilation-to-perfusion ratio; inert gas elimination technique

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POLYCYTHEMIA is commonly found in long-term residents at high altitude, but occasionally this physiological response is exaggerated. When highlanders develop excessive polycythemia, they are more hypoxemic than normal residents at the same altitude (9). Chronic mountain sickness (CMS) described by Monge in 1928 (20) is a clinical entity found in natives of high-altitude regions. It results in an excessive hematocrit accompanied by hypoxemia. It has been suggested (22) that the decrease in ventilation with increasing age and the resulting hypoxemia would accentuate the physiological polycythemia. This mechanism could explain the very high level of hematocrit found in CMS. In other studies on high-altitude natives, the alveolar-arterial P_{O_2} difference (AaD$_{O_2}$) was found to be higher in polycythemic than in normal residents (5, 13, 19). This accounted for shunt or ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatching, although it was not measured. However, when cases with pulmonary lung disease were excluded, Kryger et al. (14) did not detect an increased AaD$_{O_2}$ in subjects with pure excessive polycythemia. By scanning upper and lower lung zones of 14 patients with CMS, Ergueta et al. (5) showed a reduced perfusion of the upper lung zones, which was thought to account for the increase in physiological dead space, although they could not explain the observed hypoxemia.

The present study was therefore designed to analyze the mechanisms leading to hypoxemia in a group of native highlanders suffering from excessive polycythemia in the absence of lung or cardiovascular disease. Alveolar ideal-arterial P_{O_2} difference (AiaD$_{O_2}$) and its components, i.e., true intrapulmonary shunt, $\dot{V}_A/\dot{Q}$ mismatching, alveolar-end capillary O_2 diffusion disequilibrium, and postpulmonary shunt, were studied by measuring ventilation ($\dot{V}_A$) and perfusion ($\dot{Q}$) distributions as a function of $\dot{V}_A/\dot{Q}$ ratios by means of the inert gas elimination technique (26). In addition, the contribution of polycythemia to $\dot{V}_A/\dot{Q}$ mismatch was assessed by comparing these parameters before and after isovolemic hemodilution. All the studies were conducted at the Instituto Boliviano de Biologia de Altura in La Paz (3,650 m, 500 mmHg mean barometric pressure).

METHODS

Subjects

Eight subjects born and living in an altitude of 3,600–4,200 m were selected for the study. Their hematocrit values were well above (+3 SD) that of normal residents in La Paz (52 ± 1.5%) (8) and often close to the values reported in CMS. Those with a hematocrit >57% were included in the study. Most of the subjects complained of dyspnea and headaches, and from time to time they were treated by phlebotomy.

The clinical histories were taken by a Bolivian physician who fully explained all procedures and risks. The study was approved by the Human Subjects Review Committee, and informed consent was obtained from each participant. The clinical examination as well as the complementary investigations [chest X-ray, spirometry, electrocardiogram (ECG), and echocardiography] showed that all were free from obvious lung or cardiovascular disorders; none of the subjects smoked. Individ-

ual values for age, height, weight, hematocrit, hemoglobin concentration, and spirometric data (Collins spirometer) are shown in Table 1. Predicted values for vital capacity were those of the Communaute Européene du Charbon et de l'Acier (CECA) (3). Lefrancois et al. (16) showed that normal values for vital capacity and forced expired volume in 1 s (FEV_1), in normal high-altitude residents, were not different from the CECA values.

Protocol

A transvenous balloon-tipped catheter (7-F Swan-Ganz catheter, Edwards Laboratory, Santa Ana, CA) was inserted percutaneously into a femoral or a brachial vein. It was positioned by fluoroscopic observations of the pulmonary artery under continuous ECG monitoring. An additional 10-cm catheter (4-F Seldicath Plastimed Laboratory, St. Leu La Forêt, France) was inserted into a radial or brachial artery. Peripheral venous access was established for infusion of the inert gas mixture, which was prepared by dissolving the gases in normal glucose solution and infused by a roller pump at a constant flow rate of 5 ml/min through a 0.22-μm high-pressure Millipore filter. The mixture included SF_6, ethane, cyclopropane, halothane, ether, and acetone. All investigations were performed in the morning. After catheterization, the patients were placed in a semirecumbent position. They breathed room air through a mouthpiece and a two-way valve. The expiratory branch of the valve was connected to a wide-bore tube and a heated metal mixing box (10 liters, 40°C). The patients were connected to the mouthpiece 15 min after the start of the inert gas infusion.

Base-line data were collected when a steady state was reached, as assessed by the stability of respiratory frequency, heart rate (HR), cardiac output measured by thermodilution, and vascular pressures. A set of measurements was performed after ≥30 min of infusion. Mean atrial ($\bar{P}$at), pulmonary arterial ($\bar{P}$pa), and pulmonary capillary wedge pressures ($\bar{P}$pcw) were measured (Telco RA 8 transducers) with the midchest level taken as zero pressure. HR was measured from a single ECG lead. Cardiac output was determined by two methods: *1*) thermal dilution using a cardiac output computer (Edwards Laboratory) and *2*) inert gas mass balance from minute ventilation ($\dot{V}$E), excretion, and retention of the inert gases. Pulmonary vascular resistances (PVR) were cal-

culated as ($\bar{P}$pa − $\bar{P}$pcw)/$\dot{Q}$T, where $\dot{Q}$T represents total cardiac output. $\dot{V}$E, corrected to BTPS conditions, was calculated by collecting expired gas over 5 min in a large rubber balloon connected to the output of the mixing box. The volume was measured by emptying the rubber balloon through a 100-liter spirometer. An O_2 analyzer (Servomex model OA 150) and an infrared CO_2 analyzer (Gould capnograph mark IV) were used to measure O_2 and CO_2 fractions in the mixed expired gas. O_2 consumption ($\dot{V}O_2$) and CO_2 production ($\dot{V}CO_2$), both corrected to STPD conditions, and the respiratory exchange ratio (R) were calculated in the usual way.

Venous and arterial blood samples were withdrawn into glass syringes containing heparin and then analyzed immediately. Arterial and mixed venous pH as well as PO_2 and PCO_2 were measured with a blood gas analyzer (Il Meter model 113). PO_2 at 50% saturation (P_{50}) was calculated for each patient by tonometering two blood samples with gases containing 7% CO_2 and either 5 or 8.5% O_2. Hemoglobin concentrations were measured spectrophotometrically.

The measurement of $\dot{V}A/\dot{Q}$ distributions by the multiple inert gas technique has been described in detail elsewhere (26). The concentration of inert gases in venous and arterial blood and in expired gases was measured with two gas chromatographs: for SF_6 by an electron capture detector (model AI, Saint Cloud, France) and for the five other gases by a flame ionization detector (Delsi Instruments, model MC 30, Suresnes, France). The solubilities of the six gases were also determined. The reproducibility of these measurements was not evaluated in La Paz. However, in our laboratory in Bordeaux with the same technicians and apparatus, reproducibility, evaluated according to Wagner et al. (25) and expressed as the coefficient of variation, was 3.5% for SF_6, 4.4% for ethane, 2.9% for cyclopropane, 3.8% for halothane, 3.1% for diethyl ether, and 4.4% for acetone. These values are close to those reported by Wagner et al. (25). The representative $\dot{V}A/\dot{Q}$ distribution for blood flow and ventilation was derived from the retention and excretion curves by use of the least-squares method with enforced smoothing to minimize the effect of random experimental error (6). Intrapulmonary shunt was defined as the fraction of perfusion passing through lung units with $\dot{V}A/\dot{Q}$ ratios <0.005 and inert gas dead space as the fraction of ventilation in lung units with $\dot{V}A/\dot{Q}$ ratios >100.

TABLE 1. *Biometric, spirometric, and hematologic data*

Subject	Ethnic Origin	Age, yr	Wt, kg	Ht, cm	VC, %pred	FEV_1/FVC, %	Hemodilution, ml		Hb, g/100 ml		Hct, %	
							Phlebotomy	Dextran	Before	After	Before	After
CC	I	58	83	160					20.0		59	
CP	I	41	62	162	89	78	925	500	22.0	20.0	70	62
AB	I	65	76	158	117	61	1125	700	23.4	20.1	70	60
AF	I	26	58	161	103	80	820	500	19.0	15.6	57	47
LF	S	24	61	167	104	77	775	500	22.0	20.0	68	60
SN	I	48	74	162	90	81	775	500	20.0	15.6	57	46
PJ	S	39	68	173	107	70	825	500	21.1	18.4	64	55
GM	S	40	86	167	105	80	1275	1000	23.0	18.0	76	59
Mean ± SD		42.6±13.3	71±9.8	164±4.6	102.1±9.1	75.3±6.8	931±195	600±191	21.5±1.6	18.2±2.0	66±7	55.6±6.6

VC, vital capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; Hb, hemoglobin (measured before and after hemodilution); Hct, hematocrit (measured before and after hemodilution); I, Andean Indian; S, Spanish.

Overall ideal alveolar P_{O_2} (PA_{iO_2}) was calculated from the alveolar gas equation: $PA_{iO_2} = P_{IO_2} - [1 - (1 - R) F_{IO_2}]Pa_{CO_2}/R$, where P_{IO_2} is inspired P_{O_2}, F_{IO_2} is inspired O_2 fraction, and Pa_{CO_2} is arterial P_{CO_2}. The Pa_{O_2} expected to result from the measure $\dot{V}A/\dot{Q}$ mismatch can be computed by use of the method of West and Wagner (29). This approach requires knowledge of mixed venous and inspired P_{O_2} and P_{CO_2}, acid-base status, hemoglobin concentration, hematocrit, P_{50}, temperature, and both the O_2 and CO_2 dissociation curves. All these variables were measured for each subject, except the O_2 and CO_2 dissociation curves, which were calculated by use of Kelman's routines (29). It should be noted that this prediction of Pa_{O_2} and PA_{iO_2} and hence $AiaD_{O_2}$ is computed from the $\dot{V}A/\dot{Q}$ mismatch and intrapulmonary shunt detected by inert gas exchange. It explicitly assumes zero postpulmonary shunt and complete equilibration of P_{O_2} between alveoli and capillaries.

Hemodilution and Procedure

Thirteen to 18.4% of the estimated blood volume was removed. The blood volume was assumed to be identical to the sea level value, i.e., 8% of the body weight. Isovolemic hemodilution was performed immediately after collection of the base-line data. Blood was slowly withdrawn from an arterial catheter and simultaneously replaced with a volume of warmed 10% Dextran 40 with 5% sorbitol, which was continuously infused into the Swan-Ganz catheter. Dextran 40 was used essentially for its plasma-expanding effect. This solution is hypertonic and attracts an additional volume of fluid from the interstitial space into the blood. The infused volume was therefore adjusted to two-thirds of the blood volume withdrawn. The hemodilution was carried out over a period of ≥ 90 min to avoid hemodynamic changes. Arterial and pulmonary blood pressures, HR, and rate of ventilation were continuously monitored. After the period of hemodilution, a new mixture of the six inert gases was infused. When all gases reached equilibrium and hemodynamic and ventilatory steady state was attained, the patient was connected to the expiratory gas-mixing system as described above. Finally, samples of arterial and mixed venous blood were collected, and all the hemodynamic and ventilatory measurements were repeated. The solubilities of each of the six inert gases were determined for the new value of hematocrit.

Statistical Analysis

Student's t test for paired data was used to compare the results obtained before and after hemodilution. Results were considered significant if $P < 0.05$.

RESULTS

Base-line data. Measured gas exchange data are shown in Table 2. Pa_{O_2} was always below the lowest value measured recently (9) in La Paz in healthy nonpolycythemic highlanders (Pa_{O_2} 61.5 ± 1.1 Torr, $n = 17$). Despite a hematocrit of 68%, *subject 5* (the youngest) had a Pa_{O_2} of 56 Torr. There were some individual variations in Pa_{CO_2}. It was close to that of healthy high-

TABLE 2. *Gas exchange data*

Subject	$\dot{V}E$, l/min BTPS Before	After	f, min⁻¹ Before	After	pH$_{\bar{v}}$ Before	After	$P\bar{v}_{O_2}$, Torr Before	After	pH$_a$ Before	After	Pa_{O_2}, Torr Before	After	Pa_{CO_2}, Torr Before	After	dP_{50}, Torr	$AiaD_{O_2}$, Torr Before	After	$\dot{V}_{O_2}$, ml/min Before	After
CC	8.2	11.4	17	18	7.43	7.42	30	35	7.45	7.41	44	48	30	31	−3.8	13	15	281	255
CP	10.1	7.3	20	14	7.44	7.38	34	32	7.45	7.40	47	39	32	41	−2.9	16	14	246	231
AB	6.0	10.3	14	13	7.37	7.50	28	33	7.39	7.52	36	52	41	28	−0.7	13	14	214	180
AF	7.6	10.2	13	16	7.43	7.46	32	35	7.45	7.48	51	54	34	34	−0.3	8	5	220	240
LF	8.9	9.4	16	18	7.48	7.44	36	31	7.51	7.47	56	44	31	32	−0.3	7	15	280	234
SN	9.0	9.6	18	20	7.46	7.39	31	32	7.46	7.41	42	46	34	42	−0.4	14	5	210	234
PJ	8.5	9.2	22	19	7.40	7.39	32	33	7.41	7.40	43	43	44	39	+5.1	6	11	330	270
GM	9.6		17		7.37		36		7.38		45		37		+3.0	7			
Mean ± SD	8.5±1.3	9.6±1.3	17.1±2.9	16.8±2.6	7.42±0.04	7.42±0.04	32.4±2.8	33.3±1.5	7.43±0.04	7.44±0.04	45.6±5.6	46.6±5.2	35.5±4.6	35.3±5.4	−0.03±2.70	10.5±3.9	11.3±4.5	245±30	240±31
Difference ($n = 7$)	1.10±0.95		−0.3±1.4		0		0.6±2.2		0.01		0.9		−0.9±3			1.1±2.9		0±29	
P	<0.05		NS		NS		NS		NS		NS		NS			NS		NS	

$\dot{V}E$, minute ventilation; f, respiratory frequency; pH$_{\bar{v}}$, mixed venous pH; P$\bar{v}_{O_2}$, mixed venous P_{O_2}; pH$_a$, arterial pH; Pa_{O_2}, arterial P_{O_2}; Pa_{CO_2}, arterial P_{CO_2}; dP_{50}, P_{O_2} at 50% saturation difference; $AiaD_{O_2}$, alveolar ideal-arterial P_{O_2} difference; $\dot{V}_{O_2}$, O_2 consumption. All values, except dP_{50}, measured before ($n = 8$) and after ($n = 7$) hemodilution. Differences calculated from data on 7 subjects.

landers in La Paz (i.e., 31 ± 0.8 Torr) (9) for *subjects 1, 2,* and *5,* slightly higher for *subjects 4* and *6,* and at frankly hypercapnic levels in *subjects 3, 7,* and *8.*

In *subjects 1* and *2* and *4–6,* pulmonary vascular resistance (Table 3) was close to that of normal residents (5), but in *subjects 3, 7,* and *8* the values were similar to those observed in CMS. These three subjects had hematocrits of 70, 64, and 76%, respectively. *Subject 3* was the oldest and suffered from typical CMS. He was always drowsy and had the lowest $\dot{V}E$. His performance in the forced expiratory maneuver was poor, which could explain his slight reduction in expiratory flow rate.

The base-line retention, excretion, and partition coefficient data for all eight patients are presented in the APPENDIX. The retention data were those of minimal variance found by combining the raw data from blood and data from expired inert gas chromatographic measurements to improve the estimate of inert gas exchange (6). Before hemodilution the mean remaining sum of squares (RSS) (from the fitting of $\dot{V}A/\dot{Q}$ distribution to inert gas data) was 6.5 ± 5.7 (see Table 5), whereas for *subjects 5* and *8* it was 11.5 and 18, respectively. The somewhat high values of RSS are discussed below.

Distributions of $\dot{V}A$ and $\dot{Q}$ as a function of $\dot{V}A/\dot{Q}$ ratios are shown in Fig. 1. In the eight subjects the shunt fraction was zero, except in one subject (*3*) where only 2.8% of the cardiac output perfused unventilated areas ($\dot{V}A/\dot{Q} < 0.005$). On the other hand, the mean fractional perfusion in poorly ventilated areas ($\dot{V}A/\dot{Q} < 0.1$) was 11.6%. The results for the eight subjects are summarized in Table 5. The average dispersion estimated by the mean log SD for the group was 1.16 for the blood flow distribution and 0.63 for the ventilation distribution. The mean $\dot{V}A/\dot{Q}$ at the mean of the blood flow distribution was 0.6 and 1.12 at the mean of ventilation distribution.

The measured Pa_{O_2} for each subject was compared with his Pa_{O_2} predicted from the values of $\dot{V}A/\dot{Q}$ distribution and from the values of shunt, cardiac output, $\dot{V}E$, P_{50}, mixed venous P_{O_2} and P_{CO_2} ($P\bar{v}_{O_2}$ and $P\bar{v}_{CO_2}$), and arterial and mixed venous pH. Predicted $Pa_{O_2} = 0.81 \times$ measured $Pa_{O_2} + 7.5$ ($r = 0.90$). There was no significant difference between the two values: (predicted − measured) $Pa_{O_2} = -1.4 \pm 2.6$ Torr.

After hemodilution. The mean hematocrit of the hemodiluted subjects fell from 66.0 to 55.6% after hemodilution (Table 1).

The impact on gas exchange is shown in Table 2. Measured arterial and mixed venous P_{O_2} did not change. $AiaD_{O_2}$ remained constant. Ventilation was significantly increased (+1.1 ± 0.95 l/min) in all subjects, except in *subject 8* where it decreased slightly from 9.6 to 9.4 l/min.

Table 3 shows the hemodilution-induced change in hemodynamic parameters. The cardiac output increased significantly from 5.5 to 6.9 l/min, since both HR and stroke volume (SV) increased. PVR decreased.

The retention, excretion, and partition coefficient data for the seven hemodiluted subjects are presented in the APPENDIX.

Changes in inert gas data and distribution are shown in Tables 4 and 5. The main finding was that the retention − excretion value decreased only for ethane. Consequently, both the fractional perfusion in low $\dot{V}A/\dot{Q}$ regions and the log SD of the blood flow distribution decreased.

Under these conditions the relationship between predicted and measured Pa_{O_2} was as follows: predicted $Pa_{O_2} = 1.03 \times$ measured $Pa_{O_2} - 1$ ($r = 0.89$). As in the control situation, there was no significant difference between the two values: (predicted − measured) $Pa_{O_2} = 0.7 \pm 2.8$ Torr.

DISCUSSION

Blood Gases, $AiaD_{O_2}$, Altitude, and Polycythemia

In this study arterial blood gas values were close to those previously described in 81 native highlanders suffering from chronic polycythemia (hematocrit >57%) in the absence of pulmonary and cardiovascular disease studied in La Paz (9). In the above study, the subjects were divided into three groups: *1)* overweight subjects of any age (Pa_{O_2} 46.1 ± 5.4 Torr, Pa_{CO_2} 34.5 ± 3.8 Torr, $n = 37$), *2)* normal-weight subjects <35 yr old (Pa_{O_2} 51.8 ±

TABLE 3. *Hemodynamic data*

Subject	HR, min⁻¹		CO, l/min		SV, ml		$\bar{P}at$, mmHg		$\bar{P}pa$, mmHg		$\bar{P}pcw$, mmHg		PVR, mmHg·l⁻¹·min	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
CC			5.3						25		7		3.4	
CP	77	80	4.5	5.3	58	66	3.5	2.5	18	18	7	5	2.4	2.4
AB	70	75	5.0	6.3	71	84	7	9	35	38	5	5	6.0	5.2
AF	72	76	4.5	7.3	62	96	5	0	20	20	10	9	2.2	1.5
LF	64	68	5.5	7.2	86	106	2	−1	20	18	4	3	2.9	2.1
SN	70	72	7.4	8.2	106	114	−5	−5	30	27	5	−2	3.4	3.5
PJ	52	60	4.6	5.7	88	95	3	−2.5	23	22	3	0	4.3	3.9
GM	68	80	7.1	8.3	104	104	2	−1	48	35	1	+2	6.6	3.4
Mean	67.6	73	5.5	6.9	82	95	2.5	0.3	27.4	25.4	5.2	3.1	3.9	3.1
± SD	±7.9	±7.1	±1.2	±1.2	±19	±16	±3.8	±4.5	±10.1	±8.2	±2.8	±3.6	±1.6	±1.2
Difference ($n = 7$)	5.4±3.5		1.4±0.7		12.8±11.1		−2.2±2.7		−2.3±5		−1.9±2.6		−0.7±0.6	
P	<0.01		<0.01		<0.02		NS		NS		NS		<0.05	

HR, heart rate; CO, cardiac output calculated by mass balance applied to inert gases; SV, stroke volume; $\bar{P}at$, mean right atrial pressure; $\bar{P}pa$, mean pulmonary arterial pressure; $\bar{P}pcw$, mean pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance. All values measured before ($n = 8$) and after ($n = 7$) hemodilution. Differences calculated from data on 7 subjects.
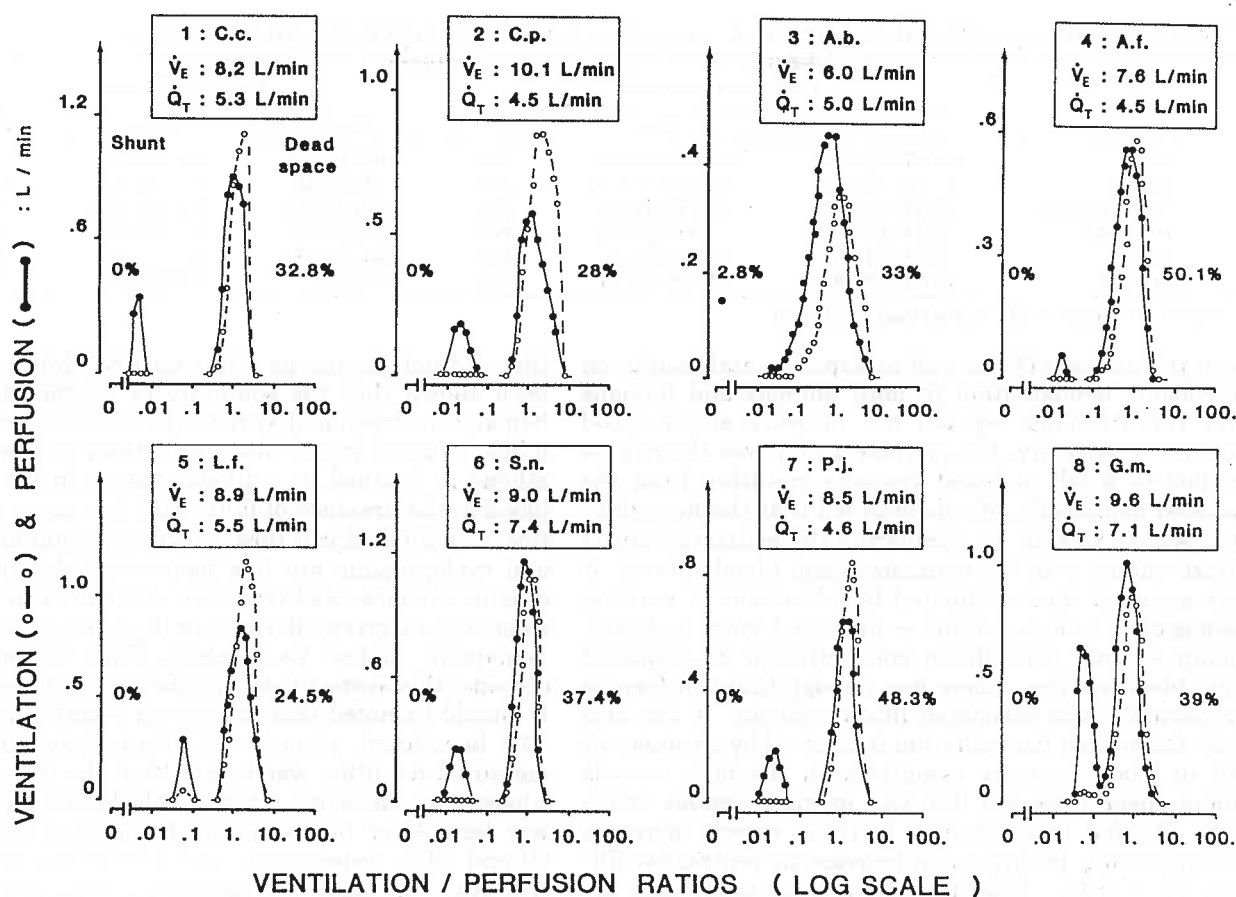
FIG. 1. Ventilation-perfusion ($\dot{V}A/\dot{Q}$) distribution patterns in 8 subjects. $\dot{V}E$, minute ventilation; $\dot{Q}T$, total cardiac output.

6.0 Torr, Pa_{CO_2} 33.0 ± 3.8 Torr, $n = 22$), 3) normal-weight subjects >35 yr old (Pa_{O_2} 46.5 ± 5.2 Torr, Pa_{CO_2} 33.0 ± 3.8 Torr, $n = 22$).

The $AiaD_{O_2}$ values measured in this study should be interpreted as a function of altitude. For a given distribution of $\dot{V}A/\dot{Q}$, $AiaD_{O_2}$ is always lower at altitude than at sea level (11). In a study performed in La Paz by Ergueta et al. (5) $AiaD_{O_2}$ measured in CMS subjects (8.6 ± 2.1 Torr) was close to that of normal healthy subjects at sea level but greater than that of healthy high-altitude residents (2.9 ± 1.1 Torr). These results have been confirmed in other studies (14, 19), but not in that of Kreuzer et al. (13), who found higher values for $AiaD_{O_2}$ in healthy residents. This apparent discrepancy may be due to the selection criteria for healthy subjects, based on objective clinical symptoms and/or physiological findings such as polycythemia and hypoxemia. In the study of Kreuzer et al. (13) physiological criteria were not taken into account: four of the eight normal subjects were almost as hypoxemic and polycythemic as the subjects with clinical symptoms of CMS. In the study of Kryger et al. (14) on humans living at 3,200 m, an increased $AiaD_{O_2}$ was only found in subjects suffering from respiratory diseases. The eight subjects of the present study were free from "apparent" cardiorespiratory disease, although they lived at a higher altitude than those in Kryger's study and had a higher hematocrit. Excluding a diffusion defect, which is discussed below, a greater heterogeneity of perfusion or

ventilation might be responsible for the increased $AiaD_{O_2}$.

Effect of Hemodilution on Respiratory Gas Exchange

Few data are available on the physiological effects of isovolemic hemodilution in subjects with excessive polycythemia living at high altitude, and in general the reported results on pulmonary gas exchange have not reached statistical significance. On three subjects in whom hematocrit was only reduced from 78 to 71%, Monge et al. (21) were unable to demonstrate improved gas exchange in spite of noticeable clinical improvement. Cruz et al. (4), in four subjects whose hematocrit was reduced from 66.5 to 58.4% after phlebotomy, suggested that the excessive polycythemia contributed to the $\dot{V}A/\dot{Q}$ mismatch. These authors demonstrated a slight improvement in gas exchange after phlebotomy. Winslow et al. (30) studied the effect of isovolemic hemodilution on O_2 transport, both at rest and during exercise, in one polycythemic native of the Peruvian Andes. In this case, hematocrit was reduced from 62 to 42%, and ventilation, cardiac output, Pa_{O_2}, and $P\bar{v}_{O_2}$ all increased. These authors suggested that $\dot{V}A/\dot{Q}$ matching was improved.

In the present study the mean hematocrit of seven subjects was reduced from 66.0 to 55.6% after hemodilution. Measured Pa_{O_2} and $P\bar{v}_{O_2}$ did not change, nor did $AiaD_{O_2}$ (Table 2), although we observed an alteration in $\dot{V}E$ and $\dot{Q}T$. This observed increase in $\dot{Q}T$ is in agreement

TABLE 4. *Partition coefficient and retention — excretion for each gas before and after hemodilution*

	λ, ml gas/ml blood BTPS			Retention-Excretion		
	Before	After	P	Before	After	P
SF$_6$	0.00873±0.0027	0.00902±0.0022	NS	0.030±0.018	0.024±0.022	NS
Ethane	0.1061±0.0118	0.1023±0.0084	NS	0.144±0.044	0.107±0.047	<0.05
Cyclopropane	0.6343±0.0478	0.6245±0.054	NS	0.234±0.059	0.202±0.068	NS
Halothane	2.347±0.195	2.345±0.219	NS	0.352±0.069	0.312±0.064	NS
Ether	11.189±1.36	11.080±0.52	NS	0.351±0.099	0.337±0.067	NS
Acetone	313.10±92.36	352.08±87.73	NS	0.436±0.1	0.409±0.051	NS

Values are means ± SD. λ, Partition coefficient.

with theoretical (17) as well as experimental results on isovolemic hemodilution in both animals and humans (10, 18). Although we did not measure either blood volume or viscosity, the increase in $\dot{Q}T$ was thought to be due to a fall in blood viscosity resulting from the reduced hematocrit. We determined that the hemodilution was isovolemic by comparing the estimated initial blood volume with the estimated final blood volume. It was assumed that (estimated blood volume × starting hemoglobin concentration) − extracted mass of hemoglobin = final hemoglobin concentration × estimated final blood volume. There was no significant difference between the two estimated blood volumes. It has also been shown that hemodilution is followed by an apparent fall in blood viscosity essentially in the large vessels where shear rates are low, i.e., in main venous stems (10). The fall in resistances in these vessels increases venous return, leading to an increase in ventricular filling, SV, and HR. Indeed, in the present study both SV and HR increased significantly, leading to a rise of 25.4% in cardiac output, whereas pulmonary resistance decreased by 22% (Table 3).

Inert Gas Method With High Hematocrit Values

Inert gas retention may depend on both $\dot{V}A/\dot{Q}$ mismatching and hematocrit-dependent solubility of inert gases. In the least-squares analysis, the RSS gives information on the exactness of fit of the model to the measured values for retentions. Two independent factors may contribute to a nonzero RSS, namely, experimental error or inaccuracy of the model. In the presence of normal experimental errors in inert gas chromatographic measurements, the usual values for RSS obtained in our laboratory or elsewhere range from 2 to 10 for both humans and animals with either normal or diseased lungs. For a normal coefficient of variation on inert gas measurement, it has been shown (6, 27) that RSS would exceed 10.6 only 10% of the time and exceed 16.8 only 1% of the time on the basis of random error. In the present study, RSS was 11.4 and 18 in *subjects 5* and *8*, respectively, and only before hemodilution. This higher than usual RSS may have been due to a slightly higher level of error in the chromatographic measurements, although a nonuniform hematocrit could also be invoked. The hematocrit in the 50 compartments of the model (i.e., in the pulmonary capillaries) was assumed to be the same as in the peripheral circulation. The effect of intrapulmonary hematocrit inequality on inert gas exchange has been evaluated by Young and Wagner (31), although

they did not discuss its effect on RSS. Moreover it has been shown that the solubility of ethane is the most hematocrit-dependent variable in humans, and its solubility is higher in red blood cells than in plasma. Thus ethane is retained to a greater extent in the perfusing blood in the presence of units with low ratios of ventilation to red blood cell flow. Since the solubilities of SF$_6$ and cyclopropane are less hematocrit dependent than ethane, the measured retention of ethane can be overestimated for a given distribution in the presence of a high hematocrit in low $\dot{V}A/\dot{Q}$ areas. Thus the model may consider this overestimation to be an experimental error. It should be noted that in *subjects 5* and *8* with 68 and 76% hematocrit, respectively, before hemodilution, the measured retention was higher than the best-fit values, whereas the measured retention of SF$_6$ and cyclopropane was less. After hemodilution, hematocrit decreased to 60 and 59%, respectively, and RSS to 6.9 and 4.2, respectively. In these two patients, a high hematocrit in low $\dot{V}A/\dot{Q}$ areas could have led to higher than usual values of RSS.

Recovered Ventilation and Perfusion Distribution in Polycythemic Patients

Before hemodilution (Fig. 1). The main finding was that these high-altitude polycythemic patients had no true shunt but had a constant level of low $\dot{V}A/\dot{Q}$ areas accounting, on average, for 11.6% of $\dot{Q}$. Consequently, the mean $\dot{V}A/\dot{Q}$ for the perfusion distribution was low (0.6) compared with normal values at sea level (24) or at simulated altitude (8). For ethical reasons, we did not carry out investigations on a control group (nonpolycythemic residents). Nevertheless, in healthy residents, $AaDO_2$ is quite small (5), and then it can be speculated that perfusion distribution would be narrow without any low $\dot{V}A/\dot{Q}$ areas.

The $P\bar{v}_{O_2}$ value in a compartment of a given $\dot{V}A/\dot{Q}$ does affect end terminal capillary PO_2 and hence influence Pa_{O_2} (28). $P\bar{v}_{O_2}$ in healthy residents in La Paz is 37.6 ± 1.1 Torr (5). Therefore $P\bar{v}_{O_2}$ can be regarded as low in most of our subjects except *subjects 5* and *8* (Table 2). This "$P\bar{v}_{O_2}$ effect" is obvious in *subject 3*, who had only 7.9% perfusion in low $\dot{V}A/\dot{Q}$ but the lowest $P\bar{v}_{O_2}$ leading to the lowest Pa_{O_2}.

To our knowledge, there are no other published reports on the distribution of $\dot{V}A/\dot{Q}$ in high-altitude residents with polycythemia by use of the multiple inert gas technique. Ergueta et al. (5), using local scanning of the upper and lower part of the lungs, found a lower perfusion

in upper zones in CMS subjects than in healthy residents at altitude. These authors concluded that the increase in $AaDO_2$ observed in their subjects was attributable to a more heterogeneous distribution of perfusion.

After hemodilution (Fig. 2). In the hemodiluted subjects, a slight but consistent improvement in $\dot{V}A/\dot{Q}$ mismatching was observed. These data are consistent with previous studies on evaluations of hematocrit values along the pulmonary vessels (2) and on the effect of reduction in peripheral hematocrit on resistance (12) and then on blood flow in different segments of the pulmonary vasculature. Unfortunately, we were unable to measure blood volume. Thus with the technique we used to replace the blood removed, we cannot rule out the possibility of a minor change in blood volume. Moreover, total ventilation and cardiac output increased simultaneously. We could not conclude that there was a specific effect of hematocrit reduction in these subjects, since there were so many simultaneous alterations in the parameters affecting gas exchange.

Measured and Predicted PO_2 According to $\dot{V}A/\dot{Q}$ Distributions

The role of $\dot{V}A/\dot{Q}$ mismatch can be discriminated from diffusion limitation in the determination of predicted Pa_{O_2} and $AiaDO_2$ by the multiple inert gas elimination technique, since inert gases are essentially unaffected by impairment in alveolar capillary diffusion (7). Thus comparison of the degree of hypoxemia and $AiaDO_2$ observed in a subject with those predicted from inert gas measurements provides an estimate of the extent of diffusion limitation. In these last conditions, as described initially by Wagner (23) in subjects with infiltrative lung diseases during exercise, predicted Pa_{O_2} is always higher than measured Pa_{O_2}. In the present study, there was no difference between measured and predicted Pa_{O_2}, and the significant difference between measured and predicted $AiaDO_2$ (3 Torr) was only due to differences between the values of PA_{O_2} calculated either from the classic alveolar gas equation or from the classic 50-compartment model of gas exchange. However, both of these models assume diffusion equilibrium in the calculation of PA_{O_2}. In the presence of a real alveolar capillary diffusion limitation, the arterial value calculated from inert gases would be higher than the measured value. Thus polycythemic patients do not seem to have a limitation in diffusion. On the other hand, since inert gases are only exchanged across the lung, postpulmonary anatomic shunts (e.g., bronchial, thebesian veins) will not affect arterial inert gas partial pressures but will reduce measured Pa_{O_2}. The absence of a significant difference between measured and predicted Pa_{O_2} would appear to rule out this mechanism as a cause of the hypoxemia in polycythemic subjects.

It was recognized by Briscoe (1) in 1959 that variable hematocrits in the blood perfusing different lung units would behave like an uneven blood flow and lead to hypoxemia. In polycythemic subjects with high hematocrit, nonuniform hematocrit could raise $AiaDO_2$ and increase hypoxemia. However, in the presence of $\dot{V}A/\dot{Q}$ mismatching, especially with a low $\dot{V}A/\dot{Q}$ mode, it has

TABLE 5. *Inert gas data*

Subject	True shunt, % Before	True shunt, % After	Blood Flow Distribution $\dot{Q}$ to $\dot{V}A/\dot{Q}=0.1$, % Before	After	Mean $\dot{V}A/\dot{Q}$ Before	After	SD Before	After	Ventilation Distribution VD/VE, % Before	After	Mean $\dot{V}A/\dot{Q}$ Before	After	SD Before	After	RSS Before	After	Predicted Pa_{O_2}, Torr Before	After	Predicted $AiaDO_2$, Torr Before	After
CC	0.0	0.0	12.3	2.5	0.50	0.94	1.6	0.9	32.8	29.6	1.0	1.5	0.4	0.6	5.8	2.1	44.2	52.9	7.5	9.1
CP	0.0	6.0	14.8	6.2	0.70	0.48	1.4	0.6	28	41.1	1.8	0.7	0.6	0.6	7.6	0.5	48.8	39.5	14.2	4.5
AB	2.8	0.7	7.9	0.7	0.45	0.92	0.9	0.3	33	29	0.9	1.0	0.7	0.3	0.5	4.8	34.8	55.5	6.5	4.1
AF	0.0	0.0	2.0	7.3	0.68	0.86	0.7	0.8	50.1	26.4	1.0	1.2	0.5	0.4	1.9	6.9	44.2	51.0	6.3	6.1
LF	0.0	0.0	5.6	2	1.00	0.6	0.8	0.8	24.5	32.8	1.4	0.9	0.5	0.6	11.5	3.0	53.3	44.0	6.8	7.0
SN	0.0	0.0	14.5	14.8	0.50	0.65	1.3	1.2	37.4	42.5	0.9	1.2	0.5	0.5	5.1	6.4	41.4	46.7	5.0	5.1
PJ	0.0	0.0	17.5	6	0.56	0.41	1.5	0.9	48.3	37.4	1.2	0.8	0.5	0.7	2.9	4.2	43.2	41.2	5.0	6.3
GM	0.0		18.3		0.40		1.1		39		0.9		0.7		18		43.1		5.4	
Mean ± SD			11.6 ±5.5	5.6 ±4.7	0.60 ±0.19	0.70 ±0.21	1.2 ±0.3	0.8 ±0.3	36.3 ±8	34.1 ±6.3	1.1 ±0.3	1.0 ±0.3	0.6 ±0.1	0.5 ±0.1	6.7 ±5.7	4 ±2.3	44.1 ±5.4	47.3 ±6.1	7.1 ±3	6.0 ±1.7
Difference ($n=7$) P			-6±6.0 <0.05		0.07±0.12 NS		-0.3±0.2 <0.01		-3.1±8.5 NS		-0.1±0.12 <0.05		-0.04±0.1 NS				3.1±4.6 NS		1.0±2.3 NS	

$\dot{Q}$ to $\dot{V}A/\dot{Q} = 0.1$, blood flow to poorly ventilated areas; $\dot{V}A/\dot{Q}$ and SD, first and second moment, respectively, of blood flow and ventilation distributions; VD, physiological dead space; $\dot{V}E$, minute ventilation; RSS, remaining sum of squares (see text); predicted Pa_{O_2} and $AiaDO_2$, arterial Po_2 and alveolar ideal-arterial Po_2 difference, respectively, calculated from inert gases. All values measured before ($n = 8$) and after ($n = 7$) hemodilution. Differences calculated from data on 7 subjects.
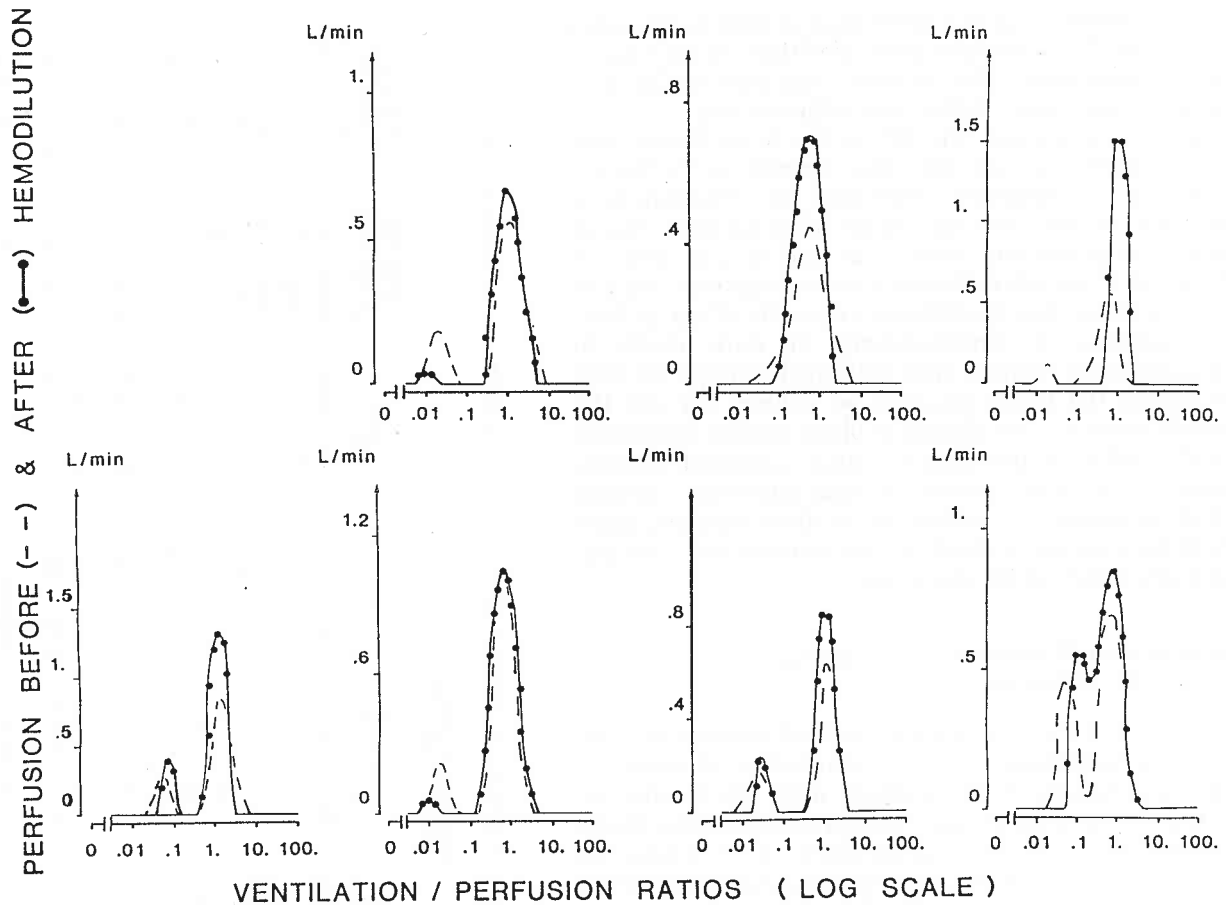
FIG. 2. Perfusion distribution as a function of ventilation-to-perfusion ratios before and after hemodilution.

been shown (31) that measured Pa_{O_2}, when hematocrit is taken into account, is often close to the predicted Pa_{O_2}, even assuming uniform hematocrit. It may be that hemodilution enhances the nonuniformity of hematocrit distribution. In the present study, hemodilution did not affect Pa_{O_2} or $AiaD_{O_2}$. A simple explanation cannot be advanced, since many variables affecting gas exchange changed at the same time.

Finally, measured Pa_{O_2} did not change significantly, although $\dot{V}A/\dot{Q}$ inequalities, as expressed by the decrease in the second moment on a log scale (log SD) of the perfusion distribution, were slightly reduced. It is unlikely that a systematic error in the P_{O_2} measurements was the source of this discordance. It is true that in five subjects, under base-line conditions, the measured Pa_{O_2} was slightly greater than the predicted one. However, this was not observed after hemodilution, which would tend to rule out the fact that a systematic error occurred. If it was the case, the predicted Pa_{O_2} calculated from $\dot{V}A/\dot{Q}$ distributions according to the method of West (29) would have reflected the improvement in $\dot{V}A/\dot{Q}$ mismatching, since $P\bar{v}_{O_2}$ remained constant. Alternatively, the lack of effect of an acute hemodilution on Pa_{O_2} could be due to the addition of two phenomena. On the one hand, O_2 transport is altered by the decrease in hemoglobin concentration. On the other hand, $\dot{V}A/\dot{Q}$ mismatch is reduced but remains at a high level. It has been shown, indeed, that Pa_{O_2} is normal with respect to PI_{O_2} in healthy

subjects under conditions of simulated altitude when mean log SD of perfusion distribution is much lower than that measured in our patients even after hemodilution. Moreover, whereas it has been demonstrated that the relationship between Pa_{O_2} and log SD of perfusion distribution is not linear at sea level (29), little is known about this relationship at altitude. Further studies with computer simulations are required to theoretically evaluate the magnitude of the reduction in $\dot{V}A/\dot{Q}$ mismatch needed to improve P_{O_2} when a high hemoglobin concentration is moderately decreased in hypoxic conditions.

Ventilation

Three of the 8 subjects had a Pa_{CO_2} above the mean value for high-altitude residents (30.5 ± 0.8 Torr). These subjects also had low $PA_{I_{O_2}}$. The hypoxemia in *subject 3* could be explained by the presence of three cumulative factors: a heterogeneous distribution of perfusion and low $P\bar{v}_{O_2}$ and low $PA_{I_{O_2}}$ resulting from hypoventilation. After hemodilution, total ventilation increased. This was solely due to an increase in tidal volume. Thus alveolar ventilation ($\dot{V}A$) was effectively increased to the same extent as the total ventilation. Moreover this increase matched the increase in cardiac output, and the mean $\dot{V}A/\dot{Q}$ for both distributions of ventilation and perfusion did not change significantly. In *subject 4*, this increase in ventilation was evidently due to a conscious response

to the hemodilution procedure, since the Pa_{CO_2} fell from 34.5 to 28 Torr. In all the other subjects, Pa_{CO_2} did not change significantly (Table 2), and ventilation was assumed to be matched to metabolism. Moreover the absence of an increase in $\dot{V}E$ would have shifted the distribution of perfusion as a function of $\dot{V}A/\dot{Q}$ to the left. This mechanism, in the presence of a reduced hemoglobin concentration, would lead to a more marked hypoxemia and hypercapnia. Both factors in a subject at normal atmospheric pressure would increase the respiratory drive. However, polycythemic highlanders are known to be particularly insensitive to hypoxemia (15). It may be that hemodilution increases blood circulation in the carotid body and enhances sensitivity to hypercapnia and/or hypoxemia. The fall in arterial O_2 content might stimulate arterial chemoreceptors, although this would

be in disagreement with the general view that the fall Pa_{O_2} is the only hypoxemic stimulus. It should be note that *subject 3*, with the lowest ventilation and the grea est hematocrit, increased $\dot{V}E$ from 6.0 to 7.3 l/mi (21.5%).

Conclusion

The hypoxemia observed in subjects suffering fro: high-altitude excessive polycythemia was largely attri! uted to an increase in blood flow perfusing poorly vent lated areas but without true intra- or extrapulmonai shunt. Hypoventilation and a low $P\bar{v}_{O_2}$ value may al: play a part, whereas hematocrit maldistribution, present, probably only has a small effect.

APPENDIX

Partition Coefficient, Retention, Excretion, and Weight Data for Six Cases

Subject	Variable	SF$_6$	Ethane	Cyclopropane	Halothane	Ether	Acetone
				Before hemodilution			
CC	λ	0.00680	0.09795	0.60766	2.36717	8.71	209.05
	R	0.06749	0.20785	0.46154	0.75289	0.90796	0.99648
	E	0.00509	0.06223	0.26242	0.46914	0.64274	0.58992
	Wt	189.341	132.496	80.155	93.837	234.360	6,057.402
CP	λ	0.01264	0.12822	0.68399	2.18065	13.0477	487.598
	R	0.05116	0.20974	0.42525	0.69833	0.91024	0.99756
	E	0.00669	0.05652	0.21929	0.36695	0.65329	0.66242
	Wt	237.188	119.616	76.388	79.209	250.659	9,297.619
AB	λ	0.01188	0.11927	0.71925	2.55834	12.70519	287.2438
	R	0.06532	0.26033	0.59592	0.82455	0.95311	0.99789
	E	0.01161	0.09221	0.30377	0.46913	0.62272	0.63289
	Wt	192.983	111.696	75.612	120.229	444.406	10,871.991
AF	λ	0.00617	0.09735	0.59494	2.30764	11.53818	267.27103
	R	0.01304	0.14590	0.45228	0.75515	0.93151	0.99723
	E	0.00362	0.04939	0.19355	0.33561	0.46940	0.43954
	Wt	377.117	187.275	79.148	92.482	301.776	·7,808.889
LF	λ	0.00905	0.10740	0.65436	2.47352	11.15330	414.65106
	R	0.00980	0.12531	0.37374	0.69304	0.89831	0.99742
	E	0.00556	0.05826	0.25417	0.47094	0.70350	0.66334
	Wt	389.104	211.575	85.639	79.568	208.767	8,036.160
SN	λ	0.00721	0.10547	0.63102	2.52860	10.70484	245.33234
	R	0.04139	0.22498	0.48785	0.78489	0.93537	0.99747
	E	0.00568	0.06714	0.26545	0.44675	0.56829	0.50940
	Wt	251.083	126.440	79.769	106.374	317.473	7,730.673
PJ	λ	0.00552	0.099909	0.59727	2.39362	10.31654	285.96738
	R	0.03578	0.21523	0.45985	0.72264	0.91729	0.99690
	E	0.00286	0.4183	0.17353	0.35710	0.45895	0.47650
	Wt	311.174	120.705	70.889	83.240	245.144	6,310.140
GM	λ	0.01058	0.09452	0.58627	1.97141	11.34673	307.70764
	R	0.04072	0.25621	0.52989	0.80738	0.95025	0.99821
	E	0.01003	0.06948	0.27238	0.37527	0.55790	0.54439
	Wt	276.960	109.451	77.355	105.290	402.317	12,114.122
				After hemodilution			
CP	λ	0.01309	0.10203	0.62756	2.20774	11.78363	315.35876
	R	0.02609	0.11980	0.38868	0.68553	0.90666	0.99643
	E	0.00741	0.05222	0.22307	0.40369	0.63956	0.65459
	Wt	333.224	214.952	88.362	77.495	214.697	5,120.178

Continued

Subject	Variable	SF$_6$	Ethane	Cyclopropane	Halothane	Ether	Acetone
AB	λ	0.00866	0.10390	0.63298	2.29678	10.48133	316.718
	R	0.08037	0.24480	0.58230	0.81937	0.95180	0.99838
	E	0.00860	0.08473	0.28552	0.44802	0.54559	0.55364
	Wt	159.369	119.058	76.397	120.849	428.938	12,535.539
AF	λ	0.00618	0.09741	0.59527	2.30892	11.54447	267.41925
	R	0.01499	0.10375	0.38813	0.71849	0.92036	0.99681
	E	0.00435	0.06235	0.26015	0.46424	0.65665	0.60992
	Wt	367.832	255.393	87.666	88.160	259.242	6,156.438
LF	λ	0.01011	0.11391	0.69786	2.75091	10.98561	492.68671
	R	0.01697	0.14566	0.41510	0.73059	0.91995	0.99816
	E	0.00695	0.06804	0.28539	0.51817	0.62255	0.64165
	Wt	360.502	193.214	78.567	82.969	246.046	10,168.226
SN	λ	0.00953	0.09391	0.56435	2.13099	11.17413	462.31552
	R	0.02394	0.15081	0.45399	0.76254	0.93590	0.99853
	E	0.00807	0.06923	0.26752	0.43931	0.62180	0.59043
	Wt	341.074	177.696	78.651	99.242	314.562	13,589.306
PJ	λ	0.00711	0.11234	0.68853	2.52763	11.23390	310.24600
	R	0.02899	0.20241	0.45168	0.75037	0.92345	0.99697
	E	0.00409	0.05301	0.22336	0.37330	0.50880	0.55671
	Wt	314.670	138.483	79.368	91.154	273.318	7,036.477
GM	λ	0.00851	0.09276	0.56514	2.19448	10.36156	299.80664
	R	0.02655	0.22896	0.55034	0.80882	0.94996	0.99839
	E	0.00882	0.07617	0.27064	0.44680	0.55220	0.51364
	Wt	326.896	121.437	78.017	114.135	412.650	12,453.050

λ, Blood gas partition coefficient; R, retention; E, excretion; Wt, weight (i.e., inverse of square root of minimal variance of retention estimated from combined retention and excretion data). No data for *subject CC* after hemodilution.

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